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Case report

Intravitreal dexamethasone implant for a vitrectomized eye with diabetic macular edema

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ABSTRACT

A 71-year-old man suffered from diabetic vitreous hemorrhage in his left pseudophakic eye. He received 20-gauge pars plana vitrectomy and removal of taut posterior hyaloid traction in June 2011. Spectral-domain optical coherence tomography demonstrated cystoid macular edema 1 month after the operation. The macular edema did not respond to macular grid laser. Intravitreal bevacizumab (1.25 mg) was injected, which was effective for managing diabetic macular edema initially. The edema recurred 3 months following the bevacizumab injection. Subsequent intravitreal triamcinolone 1 mg also failed to treat the macular edema. Ozurdex, a dexamethasone implant, was injected intravitreally in January 2012. The central foveal thickness decreased, and visual acuity improved. The effect persisted for 6 months. There was no systemic or ocular adverse event during the follow-up period. This intravitreal dexamethasone implant could be helpful for diabetic macular edema in vitrectomized eyes.

1. Introduction

Diabetic retinopathy is a common and specific microvascular complication of diabetes mellitus.[1] Diabetic macular edema (DME) is a manifestation of diabetic retinopathy that produces loss of central vision and is now the most common cause of moderate vision loss in diabetic patients.[2] The pathophysiology of DME involves both the presence of inflammation and angiogenic stimulant regarding vascular endothelial growth factor (VEGF).[2] Corticosteroid treatment has been shown to have a beneficial effect on DME.[3] The probable mechanisms involved are an increase in tight-junction proteins that diminishes vessel leakage by anti-inflammatory activity, and angiostatic properties through inhibition of VEGF.[4]

Dexamethasone is a potent corticosteroid. The Ozurdex (Allergan, Inc., Irvine, CA, USA), intravitreal dexamethasone implant consists of a biodegradable copolymer of polylactic-co-glycolic acid containing micronized dexamethasone 0.7 mg. It was developed to deliver sustained levels of preservative-free dexamethasone. Ozurdex has been approved for treatment of macular edema after retinal vein occlusion and noninfectious uveitis by the Food and Drug Administration in the USA.[5,6] This dexamethasone implant has been shown to be effective in the treatment of DME.[7–9]

In this article, we report the effect and safety profile of single intravitreal dexamethasone implant in a vitrectomized eye with diabetic macular edema. A literature review indicates that this is the first case report in Taiwan.

2. Case report

A 71-year-old man had type 2 diabetes mellitus that was under regular medical control. He suffered from severe nonproliferative diabetic retinopathy and underwent panretinal laser photocoagulation in both eyes. Subsequent phacoemulsifications and foldable acrylic intraocular lens-in-the-bag insertions were also performed in both eyes. Vitreous hemorrhage and taut posterior hyaloid traction occurred 3 months after the cataract operation in the left eye. He received conventional 20-gauge pars plana vitrectomy (Accurus; Alcon Laboratories Inc., Fort Worth, TX, USA), removal of adherent posterior hyaloid surface on the surface of the retina, supplement retinal photocoagulation using diode laser (Iris Medical Instruments, Mountain View, CA, USA), and placement of 15% C_3F_8 in June, 2011. We added cryotherapy of the anterior retina and

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sclerotomy sites (Mira, Uxbridge, MA, USA) at the end of the surgery, because a prior randomized study concluded that the procedure was helpful for inhibition of fibrovascular ingrowth near vitreous base and sclerotomies and prevention of recurrent vitreous hemorrhage after diabetic vitrectomy.[10] Spectral-domain optical coherence tomography (RTVue; Optovue, Fremont, CA, USA) revealed cystoid macular edema; central foveal thickness (CFT) in the central 1-mm area was 541 μm (Fig. 1A). His best-corrected visual acuity (BCVA) was 20/800. There was no focal leaking microaneurysm within the macula. Macular grid pattern double-frequency yttrium–aluminum–garnet laser (Alcon Laboratories Inc.) was administered according to the protocol previously described.[11] The macular edema did not respond to macular laser photocoagulation.

Intravitreal bevacizumab (Genentech, San Francisco, CA, USA) 1.25 mg was administered to manage the macular edema in August 2011. The CFT decreased to 372 μm, but some cystoid change persisted 1 month following the injection (Fig. 1B). His BCVA improved to 20/100. Three months after the bevacizumab injection, macular edema recurred (Fig. 1C). The BCVA deteriorated to 20/200, and the CFT became 418 μm. The patient refused to undergo subsequent intravitreal bevacizumab because he subjectively did not feel improvement of vision. Intravitreal triamcinolone 1 mg (Kenacort; Kitazawa Inc, Taipei, Taiwan) was injected subsequently. The edema persisted. His BCVA was 20/200, and the CFT was 424 μm at the 1-month follow-up examination (Fig. 2A).

A dexamethasone implant was injected intravitreally in January 2012. The patient was prepared in the operating room. We used proparacaine drops as topical anesthesia and subconjunctival injection of 2% lidocaine into the temporal lower quadrant. The skin and conjunctival sac was disinfected by povidone–iodine. The cap was carefully removed from the 22-gauge applicator. The safety tab was pulled straight off the applicator. The long axis of the applicator was held parallel to the limbus, and the sclera was engaged at an oblique angle with the bevel of the needle 3.5 mm away from the limbus. The needle tip was advanced within the sclera for about 1 mm, then redirected towards the center of the eye and advanced until penetration of sclera was completed and the vitreous cavity was entered. The actuator button was slowly depressed until an audible click was noted, and the needle was then removed. The tetracycline ointment was placed into the conjunctival sac. The eye was patched for 1 day. There were no cells and flares in the anterior chamber and vitreous cavity, and the Ozurdex implant was seen in the inferior part of vitreous cavity (Fig. 3). The patient was instructed to instill one drop of 0.3% norfloxacin into the injected eye four times daily for 3 weeks.

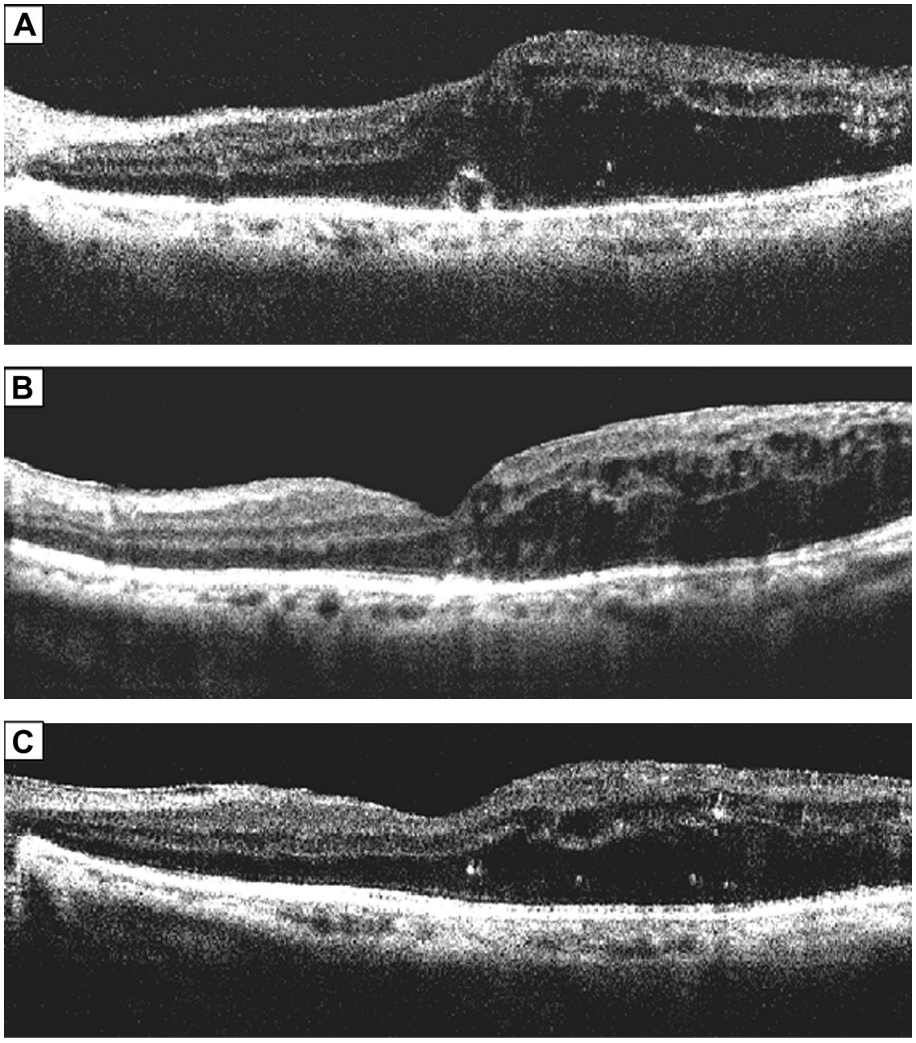

Fig. 1. Spectral-domain optical coherence tomography shows: (A) severe macular edema with cystic change; (B) macular edema partial subsidance 1 month after intravitreal bevacizumab; and (C) macular edema recurrence 3 months after intravitreal bevacizumab.

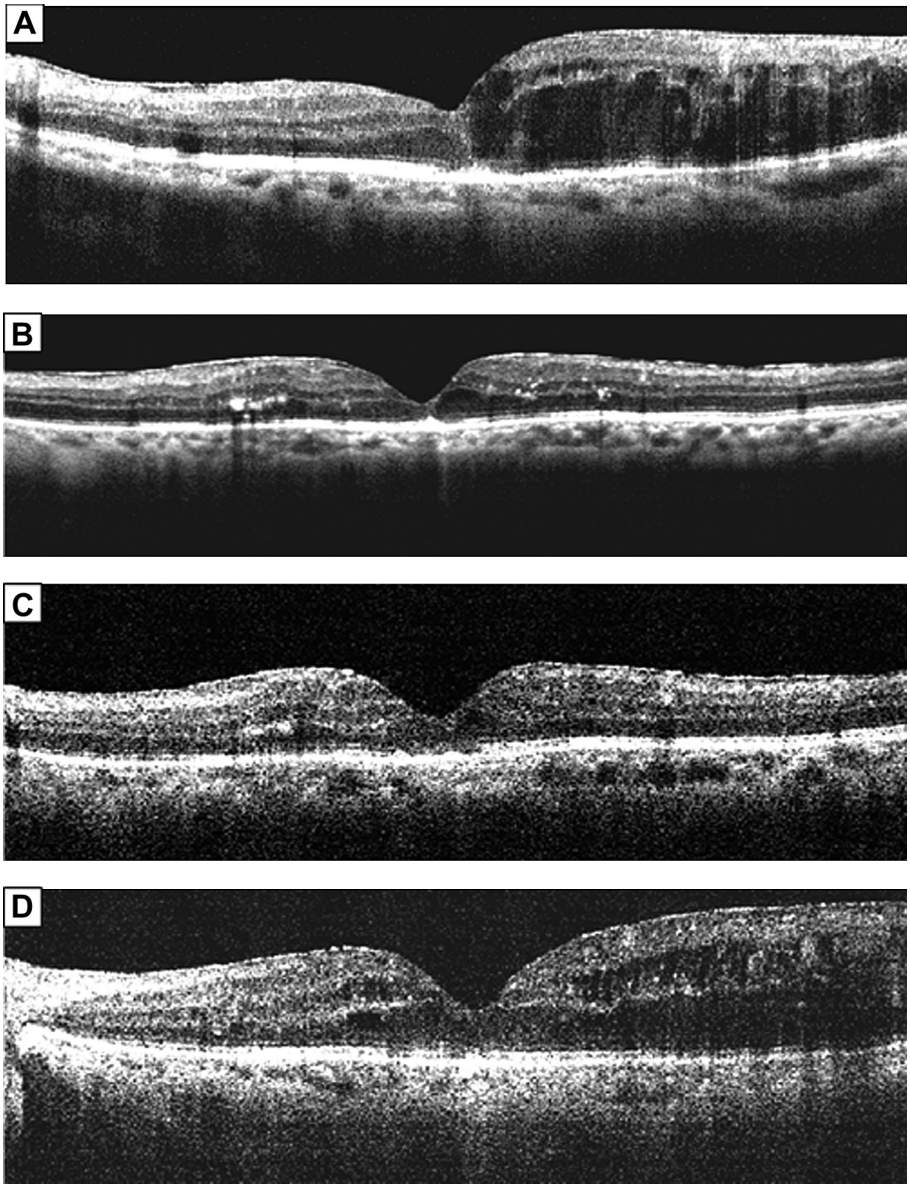

Fig. 2. Spectral-domain optical coherence tomography shows: (A) macular edema with cystic change persists 1 month after intravitreal triamcinolone acetonide; (B) macular edema completely resolved 1 month following intravitreal Ozurdex; (C) macular edema improving 3 months following Ozurdex injection; and (D) macular edema with cystic change recurrence 6 months after Ozurdex injection.

The CFT decreased to 327 μm, 281 μm, 286 μm, 294 μm, 300 μm, and 320 μm, and his BCVA improved to 20/50, 20/50, 20/60, 20/60, 20/100, and 20/100 at 1 month, 2 months, 3 months, 4 months, 5 months, and 6 months, respectively, following the injection (Fig. 2B–D), respectively. However, some cystic changes were observed after 4 months. Intraocular pressure (IOP) was normal both prior to and after the injections. There were no local complications, such as sterile endophthalmitis, elevated intraocular pressure, or systemic effect, noted during the follow-up period.

3. Discussion

Several treatments have been proposed for DME. Conventional treatment mainly involves macular laser photocoagulation.[3,11] Triamcinolone, a long-acting corticosteroid, has an anti-inflammatory effect. A systematic review of four randomized controlled trials for refractory DME treated by intravitreal triamcinolone 4 mg demonstrated that triamcinolone injection was more effective than placebo for visual improvement at 3 months, but the benefit was no longer significant at 6 months.[12] Another randomized trial found that there was an initial beneficial effect of intravitreal triamcinolone 4 mg on patients with DME at 4 months compared with a 1-mg dose or with macular laser.[3] However, the benefit diminished thereafter and, at 3 years, anatomical and functional results were better in the laser group than in the triamcinolone groups (1 mg and 4 mg, respectively).[3] Some of patients did not respond to either macular laser or triamcinolone.[3] Both triamcinolone doses, especially the 4-mg dose, were associated with an increased incidence of elevated IOP.[3]

Bevacizumab is a full-length recombinant humanized monoclonal antibody directed against the VEGF. Intravitreal bevacizumab is employed to lower the intraocular VEGF level, and has been found to reduce DME temporarily.[1,4] A multicenter study showed that repeated intravitreal bevacizumab 1.25 mg significantly

Fig. 3. The dexamethasone implant observed in the vitreous cavity on the next day after injection.

improved visual acuity and decreased macular thickness up to 24 months.[4]

Dexamethasone is a potent corticosteroid, with six-times more anti-inflammatory activity than triamcinolone. However, the short intraocular half-life of dexamethasone makes this approach difficult for clinical use. The dexamethasone implant can maintain the intravitreal therapeutic level by sustained release of the drug for 6 months without retinal toxicity after a single injection.[5] In a randomized clinical study, Ozurdex injection demonstrated superior anatomical and functional outcomes in macular edema of patients with branch or central retinal vein occlusion than the sham group in a 12-month interval.[5] The most common adverse reaction is elevation of IOP. Nearly 32% of eyes in the prior study had at least a 10-mmHg increase in IOP. Intravitreal dexamethasone implant has been shown to be beneficial in the treatment of DME.[7–9] A case series study collected nine eyes with persistent DME undergoing intravitreal injection of anti-VEGF, corticosteroids, or macular laser.[7] Following Ozurdex injections, improvement in visual acuity and macular thickness was found in the first days after the administration. Such improvement was maintained until the fourth month.[7] Another study included 18 eyes with recalcitrant DME receiving prior macular laser and/or intravitreal anti-VEGF injections.[9] An increase of visual acuity and a decrease of macular thickness were noted from 1 month to 4 months after intravitreal dexamethasone implant.[9]

Drug diffusion and clearance from the vitreous cavity is more rapid in vitrectomized eyes, limiting drug exposure to the retina and reducing treatment success and options.[8] Intravitreal pharmacologic treatment of posterior segment disease may be less effective in vitrectomized eyes. Studies in monkeys have shown that the vitreous half-life of bevacizumab is shorter in vitrectomized eyes compared with nonvitrectomized eyes.[13] Studies in rabbits have also revealed that intravitreal triamcinolone decreases more rapidly in the vitrectomized eye than in the nonvitrectomized eye.[14] Vitrectomy has also been shown to affect the intraocular concentration of triamcinolone after intravitreal injection in human eyes: elimination of triamcinolone from the aqueous humor after a single intravitreal injection was accelerated in a vitrectomized patient compared with nonvitrectomized patients.[15] In a human study, 3-monthly intravitreal bevacizumab had no effect on 11 vitrectomized eyes with DME.[16] The authors suggested that the lack of efficacy of bevacizumab might be related to faster clearance and subtherapeutic concentrations of bevacizumab in vitrectomized eyes.[16] Sustained-release delivery with the dexamethasone implant can maintain the vitreous concentration over time to a similar extent in vitrectomized and nonvitrectomized eyes of rabbits.[17] A multicenter study enrolled 55 vitrectomized eyes with DME undergoing prior anti-VEGF, triamcinolone, or macular laser therapy.[8] Treatment with dexamethasone intravitreal implant led to statistically and clinically significant improvements in both vision and vascular leakage for 6 months.[8] Increases of IOP was found in 17% of study eyes, initiating temporary medical control. No patient required a laser or surgical procedure to control IOP.[8]

In the present case, macular laser was not helpful to treat DME. Two prior randomized studies discovered that the maximal effect occurred at 1 month after intravitreal triamcinolone for DME in visual improvement and macular thickness reduction.[18,19] Our patient failed to respond to intravitreal triamcinolone either anatomically or functionally at 1 month and 2 months following the injection. The subsequent visual improvement after intravitreal Ozurdex cannot be due to triamcinolone. We used intravitreal 1-mg triamcinolone rather than standard 4-mg dose for the edema in order to avoid postinjection ocular hypertension. In spite of the lack of an IOP rise, the failure of triamcinolone might be due to the low dose or to faster clearance of the drug in this vitrectomized eye. Comparing the results 1 month following the treatments, visual acuity improved by one and three lines in the Snellen chart, CFT decreased to 372 μm with some cystoid changes and to 327 μm with normal macular contour after intravitreal bevacizumab and the dexamethasone implant. The macular edema recurred 3 months and 6 months after intravitreal bevacizumab and the dexamethasone implant. The macular edema showed better and longer response in dexamethasone implant than in bevacizumab. These observations might be associated with accelerated elimination and suboptimal intravitreal concentration of bevacizumab after the vitrectomy, and the property of slow release and maintaining a therapeutic level in the dexamethasone implant.

In conclusion, a single intravitreal injection of Ozurdex was effective for persistent DME over 6 months in a vitrectomized eye receiving prior anti-VEGF, corticosteroids, and macular laser. There was no systemic or ocular adverse event after the injection.

References

1. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. *Lancet* 2010;**376**:124–36.
2. Nguyen QD, Tatlipinar S, Shah SM, Haller JA, Quinlan E, Sung J, et al. Vascular endothelial growth factor is a critical stimulus for diabetic macular edema. *Am J Ophthalmol* 2006;**142**:961–9.
3. Diabetic Retinopathy Clinical Research Network, Beck RW, Edwards AR, Aiello LP, Bressler NM, Ferris F, et al. Three-year follow up of a randomized trial comparing focal/grid photocoagulation and intravitreal triamcinolone for diabetic macular edema. *Arch Ophthalmol* 2009;**127**:245–51.
4. Arevalo JF, Sanchez JG, Wu L, Maia M, Alezzandrini AA, Brito M, et al. Primary intravitreal bevacizumab for diffuse diabetic macular edema: the Pan-American Collaborative Retina Study Group at 24 Months. *Ophthalmology* 2009;**116**:1488–97.
5. Haller JA, Bandello F, Belfort R, Blumenkranz MS, Gillies M, Heier J, et al. Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion: twelve-month study results. *Ophthalmology* 2011;**118**:2453–60.
6. Lowder C, Belfort R, Lightman S, Foster CS, Robinson MR, Schiffman RM, et al. Dexamethasone intravitreal implant for noninfectious intermediate or posterior uveitis. *Arch Ophthalmol* 2011;**129**:545–53.
7. Zucchiatti I, Lattanzio R, Querques G, Querques L, Turco CD, Cascavilla ML, et al. Intravitreal dexamethasone implant in patients with persistent diabetic macular edema. *Ophthalmologica* 2012;**228**:117–22.
8. Boyer DS, Faber D, Gupta S, Patel SS, Tabandeh HY, Li XY, et al. Dexamethasone intravitreal implant for treatment of diabetic macular edema in vitrectomized patients. *Retina* 2011;**31**:915–23.
9. Rishi P, Rishi E, Kuniyal L, Mathur G. Short-term results of intravitreal dexamethasone implant (OZURDEX_) in treatment of recalcitrant diabetic macular edema: a case series. *Oman J Ophthalmol* 2012;**5**:79–82.
10. Yeh PT, Yang CM, Yang CH, Huang JS. Cryotherapy of the anterior retina and sclerotomy sites in diabetic vitrectomy to prevent recurrent vitreous hemorrhage: an ultrasound biomicroscopy study. *Ophthalmology* 2005;**112**:2095–102.

11. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early treatment diabetic retinopathy study report number 1. *Arch Ophthalmol* 1985;**103**:1796–806.
12. Yilmaz T, Weaver CD, Gallagher MJ, Cordero-Coma M, Cervantes-Castaneda RA, Klisovic D, et al. Intravitreal triamcinolone acetonide injection for treatment of refractory diabetic macular edema: a systematic review. *Ophthalmology* 2009;**116**:902–13.
13. Kakinoki M, Sawada O, Sawada T, Saishin Y, Kawamura H, Ohji M. Effect of vitrectomy on aqueous VEGF concentration and pharmacokinetics of bevacizumab in macaque monkeys. *Invest Ophthalmol Vis Sci* 2012;**53**:5877–80.
14. Chin HS, Park TS, Moon YS, Oh JH. Difference in clearance of intravitreal triamcinolone acetonide between vitrectomized and nonvitrectomized eyes. *Retina* 2005;**25**:556–60.
15. Beer PM, Bakri SJ, Singh RJ, Liu W, Peters 3rd GB, Miller M. Intraocular concentration and pharmacokinetics of triamcinolone acetonide after a single intravitreal injection. *Ophthalmology* 2003;**110**:681–6.
16. Yanyali A, Aytug B, Horozoglu F, Nohutcu AF. Bevacizumab (Avastin) for diabetic macular edema in previously vitrectomized eyes. *Am J Ophthalmol* 2007;**144**:124–6.
17. Welty D, Kuppermann BD, Chang-lin JE. *Dexamethasone posterior segment drug delivery system: pharmacokinetics in vitrectomized and non-vitrectomized eyes. Paper presented at 25th Annual Meeting of the American Society of Retina Specialists*; 2007. Indian Wells, CA. Abstract 3597.
18. Cardillo JA, Melo Jr LA, Costa RA, Skaf M, Belfort Jr R, Souza-Filho AA, et al. Comparison of intravitreal versus posterior sub-tenon's capsule injection of triamcinolone acetonide for diffuse diabetic macular edema. *Ophthalmology* 2005;**112**:1557–63.
19. Diabetic Retinopathy Clinical Research Network, Googe J, Brucker AJ, Bressler NM, Qin H, Aiello LP, et al. Randomized trial evaluating short-term effects of intravitreal ranibizumab or triamcinolone acetonide on macular edema following focal/grid laser for diabetic macular edema in eyes also receiving panretinal photocoagulation. *Retina* 2011;**31**:1009–27.